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March 11, 1998

Dockets Management Branch  
Food and Drug Administration  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

Re: Translation of Attachment to February 20, 1998  
Supplemental Submission by Pharmanex, Inc.  
Docket No. 97P-0441

Dear Sir or Madam:

In order to facilitate the agency's review, enclosed please find a translation of Attachment A to Pharmanex's February 20, 1998 Supplemental Submission to the above-referenced Docket (Lin, C.Y., 1994. *Development and Changes of Gutian Red Yeast and its Manufacturing*. 1994 International Wine Culture Symposium, pp. 40-43).

As noted in our February 20 submission, the reference, which documents the history of the production of what the author refers to as "Red Qu" products by one major Chinese producer, supports the point that vinegar has commonly been employed in the production of "Red Qu" products. More generally, the article also provides substantial further support for Pharmanex's position that Cholestin™ is simply standardized traditional red yeast rice --

- ♦ The steps taken by this producer to modernize the production of "Red Qu" products are no different in principle from the modern controls instituted by Pharmanex, yet still result in the production of the traditional product.
- ♦ One form of red yeast rice product -- referred to as "Light Qu" in the reference and distinguished from the wine and pigmentation products -- is used for both food and health purposes. The author notes that the differences between the various products "are mainly in fungus types, fermentation period, and the amount of water added." The article specifically notes that in the Gutian facility "Light Qu and Colored Qu can be

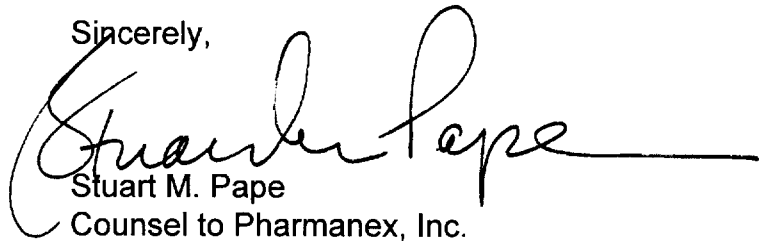
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made using a single high color value pure fungus, have (sic) fermentation periods of 7 days and 8 days, and water is added at 4 and 5 days, respectively." Although production methods may vary by facility, this demonstrates that it is common to vary the yeast strains, fermentation periods and other variables in red yeast rice production, and that the use of a pure fungal strain is not unusual or unprecedented.

Sincerely,



Stuart M. Pape  
Counsel to Pharmanex, Inc.

Enclosure

cc: Michael A. Friedman, M.D.  
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[cover]

**'94 International Wine Culture  
Symposium  
Proceedings**

Zhou Li Ping, Chief Editor

## Developmental Changes and Production Process of Gutian Red Qu (Astragalus)

Lin Zhang Yong

There is a long history in China of the preparation of Red Qu (Astragalus) used as a sugar fermentation additive for yellow rice wine and as a food coloring additive. Before the Tang Dynasty, [illegible] in "Record of Qing Yi" refers to "cooking meat in Red Qu". There are references to Red Qu in "Record of the Luoyang Ka Lan", of the Northern Wei Period. Su Dong Po's poetry from the Northern Song Dynasty speaks of "the remaining enemy's unique local specialties, such as the recorded vinegar and sugar of Red Qu". In the famous Song works of poetry, there is "evening wine poured, red as a peony" and "one desires to drink of the Red Qu wine". Thus, one can see that the appearance of Red Qu and its use in making wine has over a thousand years of history. This is a part of China and the Chinese people's precious inherited craft and artistry.

Gutian, Fujian is one of the places where Red Qu is grown and prepared. Originally made by the peasants themselves, it later developed into a cottage industry, and then factories for industrialized production were built in the 1950's. In the years 1957-1959, more than 20 provinces and municipalities visited the Gutian Red Qu Factory to learn Red Qu manufacturing techniques. Factory personnel were sent to Shenyang and other places and techniques were taught locally. Based on this, the scale of national Red Qu manufacturing was greatly increased.

In the 1950's and 60's, the Gutian Red Qu Factory produced 500-1200 tons per year, and in the 1970's Red Qu exports achieved record levels. There were breakthroughs in production processes in the 1980's. In 1983 a mechanized rice steaming workshop was constructed. From rice grain feeding to steaming, mechanized production was realized, changing the decades old history of steaming the rice by hand, and increasing work efficiency one hundred percent. In 1984, the Qu [illegible] system was changed to ventilated pond preparation, with electric injection and temperature controls, fermentation under [illegible], and the shortening of fermentation periods from nine to six days. In 1985, the product was awarded the Province's Excellent Product Award. In 1986, the nation's first advanced application of microcomputer controlled fermentation was introduced, with materials feeding increasing 1.4 times. Red Qu technology again took a step forward, developing from mechanization to high technology.

The Red Qu brewing process is fairly complicated. The process flow is as follows:

### Aged Vinegar and Mixing Distilling Grains (Red Qu Fungus Types)

rice - clean - drip dry - steam cooking - cooling - injection - underground storage -  
Red Qu fungus planting and reproduction - turning - cake opening - water fermentation -

water fermentation 2 - water fermentation 3- post water removal fermentation - heating and drying - inspection - final production grading - warehousing

Fujian Gutian Red Qu uses many varieties of fungus for fermentation, with many traditional products with special characteristics, and a relatively complicated preparation process, which is generally divided into three steps:

#### I. Mixing Distilling Grains (Mixed Fungus Pulp)

Currently, the Gutian Red Qu Factory uses multiple Red Qu fungus varieties (aspergillomycins) and [illegible] fungi. These are separated in angled test tubes, and after cultivation in flasks, each fungus is mixed together at a particular ratio based on its fungal qualities, and cultivated in rice, making a liquid variety fungal pulp, or mixing grains.

1. Recipe: 50 kg rice, mix in 18 kg variety fungus powder

2. Method: Wash the rice and place it in the pot along with the cooking grain rice. After it is cooked, drip onto a bamboo [illegible] and rinse with cold water and then dry. Pour onto a bamboo tray. Mix ingredients and separate into two [illegible]. The following day, begin folding, to adjust the crystals and add air, causing even fermentation. Starting from the second and third days, fold once daily. It is generally usable after 15 days. (40 jin of aged vinegar is added to each barrel when using).

## II. Preparation of Aged Qu Vinegar

Qu vinegar is an important supplementary material in the preparation of Red Qu. There is a strong relationship between vinegar quality and the prepared Qu. Fujian Gutian vinegar is made by undergoing glutinous rice fermentation, alcoholization, [illegible], and aging. This kind of aged vinegar possesses a unique, strong flavor, with an acidity level above nine. When heated, the acidity is not easily dissipated, and it has a good texture, slightly vinegary against an acid background. Qu vinegar is also a local specialty of Gutian, made in three parts:

### 1. Brewing of New Old Wine

The operational method of brewing new old wine is basically similar to that of Fujian yellow rice wine. This wine's special properties and requirements are: 1) pure Red Qu is sugar fermented, with fermentation additive, and no addition of White Qu, 2) glutinous rice is used as the raw material, 3) it is made by pressing after 40-50 days, 4) if using new wine, it must not be paired with lime or heated [illegible].

Preparation recipe: 50 kg glutinous rice, 5 kg Red Qu, 75 kg water

### 2. Preparation of Mother Vinegar

Vinegar base is prepared using long grained *indica* rice (early rice), long grained red *japonica* rice or wheat as raw material. These materials must first have the husks removed, but do not need to be highly processed; unpolished rice grains are fine.

When making mother vinegar, place the unpolished rice in a bottle after washing, and cook thoroughly, without overcooking, then lay out in the sun to dry for 2-3 days. When dried, it will be similar to raw rice. Then mix in the aged vinegar portion (aged more than three years) and mix in 50 kg of glutinous rice. Wait a day before separating into barrels, adding 20-25 kg to each barrel along with 30 kg of old vinegar. After 2-3 months, this is mother vinegar.

### 3. Preparation of Aged Vinegar

Take 40 kg of new old wine prepared as described above, and add 25 kg of mother vinegar made from glutinous rice. Then mix once a week. After waiting 1-2 years for it to slowly vinegar age, one can remove the aged vinegar. Each 40 kg of old new wine yields 38 kg of aged vinegar. This kind of vinegar is Fujian Gutian Qu vinegar. Preparation of Red Qu generally uses vinegar aged more than three years.

## III. Brewing of Red Qu

### 1. Raw Materials Selection and Recipe

(1) In the preparation of Red Qu, single season rice is generally preferred. After cooking it is elastic without being sticky, absorbs relatively little water in the process of making Red Qu, and it is relatively easy with respect to work and product temperature control.

(2) Fungus types and Qu types must be re-strengthened annually, and cultivated separately, so hardy fungi are selected.

(3) Aged vinegar: acidity should reach level nine or above. Vinegar and [illegible] should meet standards of excellence.

(4) Mixing ratio: 50 kg rice, mixed distilling grain pulp 1.5 kg, Qu vinegar 0.5 kg

## 2. Production Process

(1) Wash the rice, the main aspect of rice washing is to remove the [illegible] and impurities in the rice, especially [illegible] which if not removed can cause the Qu processing temperature to experience extreme increase. At the same time, when the [illegible] are at relatively high temperature, they easily break down, creating a strange taste. [illegible] primarily make the rice grains absorb a certain amount of water, making their starch cells begin to expand and change in structure. This way, when the rice is steam cooking, it is evenly cooked throughout, both internally and externally, and the internal starches can become pasty. Generally the [illegible] [illegible] level is 25-30% of the material weight.

(2) Drip Dry: Drip drying removes the water on the surface of the rice grains. If there is an excess of water on the surface of the rice grains, there will occur a relatively long heat exchange taking place first on the exterior of the grains of rice when the rice is steam cooked. This will lead to overcooking of the rice grains.

(3) Steam Cooking: The purpose of cooling the steamed rice is to destroy the starch cell structure in the rice, make the starch pasty, and make it easier for the Red Qu fungus to transform and absorb nutrients while growing. The level of cooking required is for full and even cooking, without the rice grains being sticky, [illegible], soft and loose, and without a white core. Most automatic rice steamers operate at a pressure of 2.0 MPa, with the rice being in steaming phase for five minutes, and then undergoing a cooling phase, with a cooling fan temperature drop, for three minutes. When the product temperature drops to approximately 45 degrees Centigrade, it can undergo the mixing machine and injection.

(4) Injection: This refers to taking the cooked, reduced temperature rice, and evenly mixing in Red Qu fungus varieties, allowing the fungus to grow and reproduce in the rice. Injection temperature should not be too high or too low. When the temperature is too high, the fungii are harmed by the heat exposure and may even be unable to grow and reproduce. When the temperature is too low, it affects the accumulation temperature in the pond, making the fungii reproduce slowly, making it difficult to raise the temperature, and prolonging the “growduction” period.

(5) Pool Entry and Temperature Maintenance: This is placing the injected rice in a ventilated pool where it is piled on the bottom, which temperature is maintained at a set level. This causes the Red Qu fungii to begin to grow and reproduce (colloquially known as “growduction”). Generally there are two fermentation pools, with each pool having a capacity of 800 kg of rice. Next, the doors and windows are closed, and the temperature is maintained at above 18 degrees Centigrade. The temperature maintenance period is approximately 15-18 hours.

(6) Turning: After a set period at a maintained temperature, the Red Qu fungii have already begin growing and reproducing. The center portions grow relatively more quickly. At this point, the center product temperature is 45-48 degrees Centigrade. The temperature gradually increases because of the fungii breathing functions, and carbon dioxide is simultaneously expelled. But another part of the accumulation’s outer layer has very slow growth of fungii because of its lower temperature. In order to adjust to an even internal and external rate of growth, and at the same time remove the accumulated carbon dioxide in the middle, turning, also called “turning the cover” must be done. At this time, the cake can also be opened, spreading the outer surface into the pool, and smoothing and spreading the center portion to the two ends of the pool with a wooden board. At this point, [illegible] carbon can also be added to promote micro-organic fermentation. Temperature is maintained at approximately forty degrees Centigrade.



(7) First Water Fermentation: Generally, after accumulating for twenty hours, the Red Qu fungi is basically distributed on one surface layer of the rice, and the Qu particles appear to be dry. In order to satisfy fungi growth and reproduction needs, a sufficient amount of water must be provided to allow the Red Qu fungi to continue its internal extended reproduction, making it gradually turn red. At the same time, after dissolving in the water, the red pigment also dyes the Qu grains even more. At this point, the temperature is maintained at 38 degrees Centigrade, room temperature is maintained at approximately 20 degrees, and water added is 40%. Four to six hours after adding water, the Qu must be turned once, allowing for even fermentation.

(8) Second Water Fermentation: After adding water the first time the bacteria fermentation is accelerated, Qu material temperature increase is also accelerated, and the ventilation fan frequency is increased, taking away a great amount of water. At this point, Qu material is loose and airy, and relatively dry, requiring a second addition of water. Generally, first water addition to second water addition is separated by 10-13 hours, the amount of water added is 45%, the product temperature is maintained at 37 degrees Centigrade, and room temperature is approximately 28 degrees Centigrade.

(9) Third Water Fermentation: The third addition of water also compensates for the water loss, and is generally quite critical. It must be set based on fermentation conditions of the Red Qu. There is an eight to ten hour separation between the second and third additions of water, the amount of water added is 20%, the product temperature is maintained at 36 degrees centigrade, and room temperature is approximately 25 degrees centigrade. After adding water, it must be turned once every six hours.

(10) Post Water Removal Fermentation Period: After three water fermentations, the Red Qu rice is basically done; it has produced a great amount of red pigment both internally and externally, as well as hypha and spores, etc. At this point, the fermentation is called mature phase fermentation. Product temperature is maintained at 35 degrees Centigrade, and room temperature is approximately 22 degrees Centigrade. After twenty four hours, it can be heat dried to finished product. Finished product water content is generally controlled at  $\leq 12\%$ . All physical and chemical indices are shown below in Table 1.

Table 1 Finished Product Red Qu Physical and Chemical Indices

Type Specifi- cation	Purple Qu			Light Qu			Colored Qu		
	Special Grade	Grade I	Grade II	Special Grade	Grade I	Grade II	Special Grade	Grade I	Grade II
Item:									
Capacity (g/100 ml)		33.0 - 50.0			32.0 - 37.8			25.0 - 31.9	
Maturity Rate (%)≥	99	96	93	99	97	94	100	99	96
Moisture Content (%)≤		12			12			12	
Color Value ≥	450	350	200	800	600	450	1000	850	700
Purified [illegible] Activity (measured in glucose mg-g/hr) ≥	1000	800	600	900	700	500			

Red Qu has three different varieties; Purple Qu, Light Qu, and Colored Qu. Collected Qu is primarily used to make yellow rice wine, liquors, and medicines. Light Qu is primary used to [illegible] fermented bean curd, jellies, liqueurs, medicines, food coloring, and all types of canned meat and fish coloring preservatives. Colored Qu is primarily used to manufacture fermented bean curd, red food coloring for pickled vegetables and all foodstuffs. The differences among them in preparation are mainly in fungus types, fermentation period, and the amount of water added. Purple Qu is made using multiple fungus types, fermentation period is 6 days, and water is added 3 times. Light Qu and Colored Qu can be made using a single high color value pure fungus, have fermentation periods of 7 days and 8 days, and water is added at 4 and 5 days, respectively.